## REMARKS

Entry of the above amendments and reconsideration of the claims in the above-referenced application are respectfully requested. After entry of the above amendments, claims 1, 3-10 and new claims 15-17 are currently pending in the application. Claims 11-14 have been previously withdrawn from further consideration as being drawn to a non-elected invention.

I. Amendments to the specification and claims

The specification has been amended to replace the section title on page 12, line 21 with the more descriptive title "1. Nucleic acid tags". It is clear from a reading of this section, particularly the disclaimer in the first paragraph of the section, that the section is concerned with a description of the nucleic acid tags employed in the method rather than with a "solid support."

Claim 1 has been amended to include the following limitations:

(1) The groups of subsets of nucleic acid tags formed in steps (a) and (c) are *for participating in a first synthetic reaction and a second synthetic reaction*, respectively, as disclosed for example, on page 4, line 31 to page 5, line 5 and page 6, line 29 to page 7 line 10, and page 11, lines 3-18, and page 11, line 30 to page 12, line 8.

(2) the forming step in steps (a) is carried out by *contacting the nucleic acid tags with a plurality of first immobilized nucleotide sequences, each designed to capture a subset of said tags by hybridization between one of said tag first hybridization sequences and the associated first immobilized sequence*; and the forming step in step (c) is carried out by *contacting the nucleic acid tags with a plurality of second immobilized nucleotide sequences, each designed to capture a subset of said tags by hybridization between one of said tag second hybridization sequences and the associated second immobilized sequence*; as described, for example, on page 14, line 6 to page 15, line 15.

(3) the reacting step in (b) involves reacting the chemical reaction site in each of the tag subsets with *a selected one of a plurality of first reagents, to convert the reaction site in each tag* to a reagent-specific compound, and the reacting step in (b) involves reacting the compound intermediate in each of the tag subsets with *a selected one of a*

*plurality of second reagents*, as disclosed, for example, on page 4, line 31 to page 5 line 5, page 6, line 29 to page 7, line 10, and page 11, lines 3-17 (which applies generally to split and recombine synthetic methods for making combinatorial libraries), and page 15, line 25 to page 16, line 18.

Claims 3 and 4 were amended to clarify the nature of the first and second reagents used in steps (b) and (d) in forming a plurality or oligomers (claim 3) and compounds with substituents (claim 4).

Claim 5 was amended to incorporate the amended method steps from claim 1 into the Nth>2 reaction cycle(s), as disclosed for example, on page 12, lines 9-14.

Newly added claim 15 includes the limitation that each of the immobilized nucleotide sequences is each bound to the surface of a solid phase reagent, as disclosed for example, on page 14, 14-24.

Newly added claims 16 and 17 include the additional limitation that the reacting steps (b) and (d) include first transferring the separate subsets of tags from the immobilized sequences to a solid support, as disclosed, for example, page 16, line 1-18.

No new matter has been added by these amendments.

II. Rejection Under 35 U.S.C. § 112, first paragraph

Claims 1-10 stand rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention. This rejection is respectfully traversed in view of the following remarks.

A. Legal Standard for Written Description

In order to determine whether the written description requirement has been satisfied, it must be asked whether the description clearly allows a person of ordinary skill in the art to recognize that the inventor invented what is claimed. *In re Gosteli*, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989). The factual inquiry involved is whether the applicant conveys with reasonable clarity to those skilled in the art that, as of the filing

date sought, applicant was in possession of the invention as now claimed. *See, e.g.*, *Vas-Cath, Inc. v. Mahurkar*, 19 U.S.P.Q.2d 1111, 1117 (Fed. Cir. 1991). Possession of the invention may be shown, for example, by describing the invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention. *Lockwood v. American Airlines*, Inc., 41 U.S.P.Q.2d 1961, 1966 (Fed. Cir. 1997). "The purpose of section 112, first paragraph, is to ensure that there is an adequate disclosure of the invention for which patent rights are sought. The purpose of the description requirement is to state what is needed to fulfill the enablement criteria. These requirements may be viewed separately, but they are intertwined." *Kennecott Crop. V. Kyocera Int., Inc.*, 5 U.S.P.Q.2d 1194, 1197(Fed. Cir. 1987), *cert denied*, 486 U.S. 1008 (1988).

B. Description of the disclosed invention

The claimed invention, as clearly disclosed in the patent application (see citations below) is directed to a method of using nucleic acid tags to direct the synthesis of a combinatorial library by a split and combine synthetic strategy (see, for example, page 4, lines 15-21).

In practicing the claimed method, one starts with a set of nucleic acids, each of which includes two or more unique sequences that will dictate the particular synthetic steps that will be applied to a reaction site carried on each tag. In particular, each tag include V different reaction-site positions, and at each such position, N different sequences corresponding to N different reactions that can occur at each reaction step V. For example, and as described on page 12, line 22 to page 13, line 23, each tag may include ten different reaction positions $V_1$-$V_{10}$, corresponding to ten reaction successive steps, and ten (N) different sequences at each V position. As noted on page 13, lines 14-21, the different tag sequences—in this case, 100 different reaction-specific tag sequences (V x N) and 11 constant spacer sequences—are unique and do not cross-hybridize with one another. Each tag also includes a reaction site, as described, for example, on page 13, line 26 to page 14, line 4, at which each successive chemical reactions occur on that tag. That is, the successive chemical reactions in the synthesis

of a particular combinatorial compound on a given tag take place on the tag reaction site.

To carry out the first reaction step, the tags are "split" into a first group of nucleic acids tag subsets, e.g., 10 different subsets corresponding to the ten different sequences (N) at the "first" tag position ($V_1$) in each tag. This is done by contacting the probes with a first group of solid-phase reagents (immobilized sequences), each having a sequence that is complementary to one of the N different "first-position" sequences in the tags. In other words, the tags are divided into N subsets, where each subset is determined by the "first-position" sequence of one of the tags. This step corresponds to the "split" stage of the usual split-and combine synthesis strategy; however, in this case, the splitting is not done randomly, but dictated by the "first-position" sequences of the tags. This step is detailed, for example, on page 14, line 7 to page 15, line 8.

After this splitting step, the N different tag subsets, e.g., ten different subsets of tags, are reacted with N different reagents, where the identity of each reagent is known (dictated by) the particular tag subset, and therefore, by the particular tag sequence that determines that subset. This first coupling step, which converts the reaction site in each tag to a reagent-specific compound intermediate, is described, for example, on page 15, line 25 to page 16, line 18.

Following the first reaction step, the reacted tags are now contacted with a second group of solid-phase reagents (immobilized sequences), each having a sequence that is complementary to one of the N different "second-position" sequences in the tags (where N may or may not differ from the "first-stage" N). As above, this step again splits the tags are into a given number of subsets, e.g., 10 subsets, where each subset is now determined by the "second -position" sequence of one of the tags. This step is detailed, for example, on page 15, lines 9-15.

Each of the different "second-position" subset of tags is now reacted with one of a second plurality of reagents, a different one for each subset, as disclosed, for example, on page 16, lines 24 and 25, for split and combine methods of synthesis, as described additionally on page 11, lines 3-17.

This process of splitting the previously reacted tags into N different subsets, by hybridizing the tags with a new set of immobilized oligonucleotides, then reacting the N

new subsets of tags with N different selected reagents, is repeated until all of the reaction steps to be performed successively on the tag reaction sites are complete, as described on page 16, lines 24-25.

C. Analysis

The applicant contends that the above-noted passages in the specification clearly describe the claimed nucleic-acid directed split-and-combine method of combinatorial synthesis, as outlined above. Nowhere has the Examiner pointed to any deficiency in the application that would lead one skilled in the art to fail to appreciate how the claimed invention is carried out and what it is intended to accomplish. Since the specification clearly apprises one of skill in the art as to the nature of the invention, and how it is to be carried out, it is not seen how one skilled in the art could reach the conclusion that the applicant did not have possession of the invention at the time the application was filed. In addition, and addressing specific issues raised by the Examiner:

1. It is clear that the method contemplates producing both oligomer and small-molecule combinatorial libraries, as noted, for example, at page 5, lines 11-15, page 6, lines 16-20, page 7, lines 14-16, page 9, lines 4-9, page 11, lines 18-23, page 13, line 25 to page 14, line 4, page 16, lines 1-18, and page 18, lines 6-11.

2. The Examiner notes, on page 6 of the amendment that the specification does not teach the claimed method of tag-directed synthesis wherein the method step of attaching a reagent to the "nucleic acid" tag encompasses any type of reaction mechanism other than hybridization to form base-specific duplex." This characterization of the specification is not understood. As clearly disclosed in the specification, the hybridization reaction is used to split the tags into N different subsets, which are then chemically reacted at their reaction sites to chemically synthesize the combinatorial compound attached to each nucleic acid tag (see the discussion and citations to the specification given above).

3. The specification clearly describes the method steps of forming a second group of subsets of the reacted nucleic acid tags and reacting the compound intermediates in each of the second group of subsets formed with a second reagent (see the discussion

and citations to the specification given above).

4. The specification teaches the claimed method of tag-directed synthesis where the nucleic acid tags of the first group of subsets comprise a plurality of different first hybridization sequences, a mixture of second hybridization sequences and a chemical reaction site, and the nucleic acid tags of the second group of subsets comprise a plurality of different second hybridization sequences and a mixture of different first hybridization sequences (see the discussion and citations to the specification given above).

5. The specification teaches the claimed method of tag-directed synthesis wherein the method step of attaching a reagent to the nucleic acid tag encompasses a wide variety of reaction mechanisms other than hybridization to form a base-specific duplex (see the discussion and citations to the specification given above).

In view of these remarks, the applicant submits that the patent specification complies with the written description requirement of 35 U.S.C. §112, first paragraph.

III. Rejection Under 35 U.S.C. §112, second paragraph

Claims 1-10 stand rejected under 35 U.S.C. §112, second paragraph, for various reasons. Each of these points of rejection will be addressed below. As the examiner is aware, the test for determining whether a claim meets the definiteness requirement is "whether those skilled in the art would understand what is claimed when the claim is read in light of the specification." *Beachcombers, Intl., Inc. v. WildeWood Creative Prods.*, 31 U.S.P.Q.2d 1653,1656 (Fed. Cir. 1994), *citing Orthokinetics, Inc. v. Safety Travel Chairs, Inc.*, 1 U.S.P.Q.2d 1081, 1088 (Fed. Cir. 1986).

A. Claim 1: "the chemical reaction site in each of the subsets" of the nucleic acid tags

Claim 1 stands rejected on the grounds that "a chemical reaction site in each of the subsets of the nucleic acid tags" is indefinite because it is unclear as to the means of determining "location" of the reaction site on the "nucleic acid tag" (i.e., where on the tag is the reagent being attached).

The applicant fails to understand this rejection. The reaction site is part of the

nucleic acid tag, but its location on the tag is neither critical nor pertinent to the claimed invention. The reaction site could be at either end of the nucleic acid tag, or even attached to a non-terminal nucleic acid base, as long as the reaction site does not interfere with hybridization to the solid-phase oligonucleotides (in the step of splitting the nucleic acid tags into N subsets) and is accessible to reaction (in the reaction steps).

B. Claim 1: "the reacted nucleic acid tags"

Claim 1 further stands rejected as it is asserted "the reacted nucleic acid tags" is vague and indefinite because it is unclear if it is referring to the reagent-specific compound intermediate formed in step (b) or the product of the claimed method. Claim 1 has been amended to clarify that "the reacted nucleic acid tags" refer to the tags formed by reaction step (b).

C. Claim 1: Alleged Omission of Essential Steps

Claim 1 stands rejected as it is asserted it is incomplete for omitting the following alleged essential steps: 1) the step between step (b) and step (c) as it is asserted it is unclear as to the correlation between these steps (i.e., what happened to the reagent-specific compound intermediate); and 2) the step between step (b) and step (d) because it is asserted it is unclear as to the role in which the reagent-specific compound intermediate plays in forming the compounds of the claimed method since alleged combination of method steps (c) and (d) would produce the compounds whereas the combination of method steps (a) and (b) would produce the compound intermediate.

No essential steps have been omitted from claim 1. It is clear from the specification on, for example, page 14, line 6 to page 15, line 15, and also claim 1 that the reagent-specific compound intermediate is formed from reacting the chemical reaction sites in each of the subsets formed in (a) and, that the second group of subsets is formed from the reacted nucleic acid tags (which have a reagent-specific compound intermediate attached thereto). Therefore, it is clear from the claim what happened to the reagent-specific compound intermediate. It is also therefore clear what role the specific compound intermediate plays in forming the compounds. As recited in claim 1(d), the compound intermediates in the sequences in each of the subsets formed in (c) are reacted with a selected second reagent. There is therefore no essential material

missing from the claim, and such claim would be understood by the person of ordinary skill in the art.

D. Claim 2: "reagents"

Claim 2 stands rejected as it is asserted the term "reagents" in line 4 is indefinite because it is unclear whether this reagent refers to the "solid phase reagent" of the surface bound oligonucleotide or the reagents of claim 1 in step (b) and/or (c).

As claim 2 has been cancelled, this rejection is now moot.

E. Claim 5: "synthetic step"

Claim 5 stands rejected as it is asserted the limitation "synthetic step" does not have sufficient antecedent basis in claim 1. The amendment in claim 1 to refer to first and second synthetic steps provides an antecedent basis for this term in claim 5.

F. Claims 3 and 4: "a selected subunit" and "a selected chemical substituent"

The Examiner states that "the recitation of 'a selected subunit' of claim 3 and 'a selected chemical substituent" of claim 4 are vague and indefinite because it is unclear if the 'subunit' and 'chemical substituent' or are they referring to the reagents of claim 1 (i.e. first reagent and second reagent)." This rejection, as it is understood by the applicant, is overcome by the amendment to claim 3 and 4 which clarifies that the first and second reagents in the reaction steps (b) and (d) are subunits and substituents, respectively.

In view of the foregoing claim amendments and foregoing remarks, the applicant submits that the claims now pending in the application comply with the requirements of 35 U.S.C. §112, second paragraph.

IV. Rejection Under 35 U.S.C. §102

Claims 1 and 3-6 were rejected under 35 U.S.C. § 102(b) as being anticipated by Brenner and Lerner. [*Proc. Natl. Acad. Sci*, 89(12):5381-5383 (1992)]. Claims 1-10 were also rejected under 35 U.S.C. § 102(b) as being anticipated by U.S. Patent No. 5,604,097 to Brenner (the '097 patent). Claims 1 and 7-10 were rejected under 35 U.S.C. § 102(e) as being anticipated by U.S. Patent No. 5,962,228 to Brenner (the '228 patent). These rejections are respectfully traversed in view of the following remarks.

A. The Claimed Invention

The method of the claimed invention, as described in Section II above, includes the steps (a)-(d) as follows:

(a) forming a first group of subsets of nucleic acid tags for participating in a first synthetic reaction step, where the nucleic acid tags in each subset each has a selected one of a plurality of different first hybridization sequences, a mixture of different second hybridization sequences, and a chemical reaction site. This step is carried out by contacting the nucleic acid tags with a plurality of first immobilized nucleotide sequences, each designed to capture a subset of said tags by hybridization between one of the tag first hybridization sequences and the associated first immobilized sequence. The purpose of this step is to divide a plurality of nucleic acid tags into N subsets, each dictated by a specific "first-position" sequence in the tag.

(b) carrying out the first synthetic step by reacting the chemical reaction sites in each of the subsets formed in (a) with a selected one of a plurality of first reagents, to convert the reaction site in each tag to a reagent-specific compound intermediate on the associated tag in each subset. The purpose of this step is to chemically modify the reaction site in each tag subset in a manner dictated by the first-position tag sequence associated with that tag. In other words, the nature of the first reaction step is directed by the first-position tag sequence in a preexisting nucleic acid tag.

(c) forming a second group of subsets of the reacted nucleic acid tags formed in step (b), for participation in a second synthetic reaction step. This step is carried out by contacting the reacted nucleic acid tags with a plurality of second immobilized nucleotide sequences, each designed to capture a subset of said tags by hybridization between one of the tag second hybridization sequences and the associated second immobilized sequence. The purpose of this step is divide the once-reacted tags into N new subsets, each dictated by a specific "second-position" sequence in the tag.

(d) carrying out the second synthetic step by reacting the compound intermediate in the associated tags in each of the subsets formed in (c) with a selected one of a plurality of second reagents. The purpose of this step is to apply a different chemical modification (reaction) to each of the already-reacted reaction sites, where the particular

reaction carried out is directed by the second-position tag sequence associated with that tag. In other words, the nature of the second reaction step is directed by the second-position tag sequence in the preassembled nucleic acid tag.

From this description, one can appreciate the differences of the claimed invention over the prior art, and the advantages the method provides over prior-art tag methods. In particular, the preexisting nucleic acid tags in the present invention direct the actual reactions that are applied to the reaction site of each tag, determining the actual molecule that will be synthesized by each preexisting nucleic acid tag.

This is in contrast to each of the cited prior art references, where the nucleic acid tag is synthesized in parallel with the combinatorial molecule at each reaction step. In this prior-art method, the nucleic acid tag is used to report the sequence of reactions that have been carried out, allowing the identification of the molecule based on its synthetic history. In the prior art, however, the nucleic acid tags do not direct the synthesis of combinatorial molecules based on preexisting tag sequences. The claimed invention offers several unique advantages over the prior art:

First, since a separate nucleic acid probe is not being synthesized in parallel with the combinatorial compound, the combinatorial molecule synthesis is not constrained by particular reagents or conditions required for nucleic acid synthesis.

Second, and more importantly, the claimed method allows one to (i) isolate combinatorial molecules of interest, (ii) amplify the associated nucleic acid tags, and (iii) use the amplified tags, without requiring any knowledge of the actual sequences being amplified, to direct the synthesis of the same molecules. This allows one to successively enrich a very large population of combinatorial species, e.g., $10^{12}$ molecules, for a relatively small number of active molecules, e.g., 100, by repeated selection and resynthesis. This cannot be done (in any practical sense) by prior art methods which require amplifying and sequencing each nucleic acid tag to be resynthesized.

Finally, the claimed method allows the application of gene shuffling methods to be applied to the nucleic acid tags, to expand a combinatorial library in a particular chemical structure space.

B. The Prior art

Brenner and Lerner (PNAS) teach use of a process of two alternating parallel combinatorial syntheses to encode individual members of a large library of chemicals with unique nucleotide sequences. A PCR oligonucleotide on a solid support is first synthesized. The product is divided into two aliquots, and then a subunit is added to a linker on the support followed by simultaneous addition of an oligonucleotide sequence which encodes that subunit to the PCR oligonucleoitde. The elongated products are pooled, and again split for parallel synthesis.

Nowhere does Brenner and Lerner show or suggest any of steps (a)-(d) of claim 1, nor the purpose of any of these steps.

The Brenner '097 patent teaches methods for sorting polynucleotides using oligonucleotide tags. As described in column 3, line 33 to column 4, line 31, a polynucleotide to be sorted has an oligonucleotide tag attached, such that identical polynucleotides have the same tag and different polynucleotides have different tags. The tags are used for sorting the polynucleotides by specifically hybridizing the tags attached to the polynucleotides to their complements, which are attached to and have been synthesized on solid phase supports. Once separated, the nucleotide sequence of the polynucleotides is determined by a single base sequencing methodology.

The Brenner '097 patent also discloses combinatorial chemical library preparation in column 11, lines 38 to column 12, line 36 and as outlined in Figure 4. As seen in Figure 4 and as described in column 12, lines 1-36, a tag is formed by adding subunits S1, S2, S3, etc. to an oligonucleotide segment attached to a controlled-pore glass support. At the same time as subunits S1, S2, S3, etc. are added, the corresponding library monomers A1, A2, A3, etc. are being added. After synthesis is completed, the product is cleaved and deprotected to form a tagged library compound which undergoes a selection process (i.e., binding to a predetermined target). The tagged library compound is then sorted on a solid phase support by binding to complementary subunits, the peptide is cleaved from the tag and the tag is sequenced to determine the sequence of the peptide produced.

Nowhere does Brenner '097 show or suggest any of steps (a)-(d) of claim 1, nor

the purpose of any of these steps.

The Brenner '228 patent describes a primer walking method for DNA sequencing. In this method, rolling primers are provided that differ only in their terminal nucleotides to a primer binding site of a sequencing template so that only the rolling primer whose terminal nucleotide forms a perfect complement with the template leads to formation of an extension product. After amplifying the double-stranded extension product to form an amplicon, the terminal nucleotide, and hence the complement in the template, is identified by the identity of the amplicon. The primer binding site of the amplified polynucleotide is mutated so a subsequent rolling primer may be utilized and the steps of selective extension, amplification and identification are repeated.

One feature of the Brenner '228 invention is the capability of applying the method to many different polynucleotides in parallel by the use of oligonucleotide tags. A unique tag that is attached to each polynucleotide of a population can be copied in the process and used to shuttle sequence information to a solid phase support for detection. In this embodiment, as outlined in column 4, lines 45-59, an oligonucleotide tag is attached to each polynucleotide so that substantially all different polynucleotides have different oligonucleotide tags attached, the tags are labeled, the tags are cleaved and then sorted onto a spatially addressable array, such as a solid phase support that includes tag complements for hybridization (as described in column 13, lines 42-49 and column 14, lines 6-58) and detection. Labeling of the tags is discussed in column 13, lines 52-55, and may be accomplished by including direct or indirect attachment of radioactive moieties, fluorescent moieties, colorimeteric moieties, and chemilumuniescent markers.

Nowhere does Brenner '228 show or suggest any of steps (a)-(d) of claim 1, nor the purpose of any of these steps.

C. Analysis

"Anticipation under 35 U.S.C. § 102 requires the presence in a single prior art disclosure of each and every element of a claimed invention." *Electro Med. Sys. S.A. v. Cooper Life Sciences, Inc.,* 32 U.S.P.Q.2d 1017, 1019 (Fed. Cir. 1994).

Since none of the cited references discloses any of the steps (a)-(d) above, much

less any one step, they cannot anticipate the claimed invention. Nor would any of these references, taken singly or in combination, render claim 1 obvious, since none of the references suggests the purpose of any of the claimed step, nor the unique advantages obtained by the method (discussed in Section A above).

Claims 3-10, and new claims 15-17 define patentably over the prior art for the same reason that claim 1 does.

In view of these remarks, the applicant submits that the prior art neither anticipates the claimed invention, nor renders it obvious.

V. Conclusion

In view of the above remarks, applicants submit that claims 1, and claims 3-10 now pending in the application are now condition for allowance. Additionally, new claims 15-17 are not disclosed or suggested in any of the documents of record and are therefore also in condition for allowance. A Notice of Allowance is, therefore, respectfully requested.

If in the opinion of the Examiner a telephone conference would expedite the prosecution of the subject application, the Examiner is encouraged to telephone the undersigned attorney at (650) 833-7731.

Respectfully submitted,
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